REMARKS

The pending claims (claims 1-22) remain directed to a certain potassium channel inhibitors, compositions and related methods. Applicants affirm the election of Group I, including claims 1-17. Claims 18-22 stand withdrawn from consideration.

Claims 1 to 17 have been amended to remove the recitation of "prodrug." Claim 1 has been amended to limit the recitation of A, B and D to substituted carbon atoms consistent with the restriction requirement. Claims 3, 5, 9 and 11 also have been amended consistent with this amendment to claim 1. Claim 1 also has been amended to indicate that each of the substituents that is recited for R^2 may be optionally substituted. Support for this recitation is found in the specific definitions for each of the possible R^2 substituents found in paragraphs of the application as follows: alkyl (¶54), carbocycloalkyl (¶68), aryl (¶76), (aryl)alkyl (¶77), heterocyclo (¶69), (heterocyclo)alkyl (¶78), heteroaryl (¶71), and (heteroaryl)alkyl (¶78). No new matter is added by these amendments.

Applicant traverses the restriction between Groups I and II. The Office Action fails to justify restriction among the Markush group of substituents recited for R^2, i.e., alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, and (heteroaryl)alkyl. The different "ring systems" that the Office Action uses to justify the restriction requirement is the core structure and by the foregoing amendment, applicants have limited claims 1-17 to a single core, ring structure. Groups I and II share the same core, ring structure and thus should be examined together.

Claims 16 and 17 have been objected to as being improper dependent claims. This objection is respectfully traversed.

The Office Action contends that "a dependent claim cannot refer to another multiple dependent claim," citing MPEP §608.01(n). Applicants' undersigned representative has reviewed the cited portion of the MPEP, as well as the related portion of the Code of Federal Regulations (37 C.F.R.) and does not find any such prohibition. While one multiple dependent claim cannot be dependent upon another multiple dependent claim, that does not apply to claims 16 and 17, neither of which is a multiple dependent claim. Neither the MPEP, nor the rule, prohibits a dependent claim (single dependency) from being based on a multiple dependent claim. Withdrawal of the objection is respectfully requested.

Claims 1-15 stand rejected under 35 U.S.C. 112, second paragraph for various reasons.

This rejection is respectfully traversed.

The Office Action contends that the recitation of "prodrug" renders the claim indefinite. By the previous amendments, the term "prodrug" has been removed from the claims.

The Office Action contends that it is not clear whether R^2 can be substituted. As recited in claim 1, R^2 is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, and (heteroaryl)alkyl. Alkyl is defined in ¶54 and can be optionally substituted. Carbocycloalkyl is defined in ¶68 and can be optionally substituted. Aryl and (aryl)alkyl are defined in ¶¶ 76 and 77, respectively, and can be optionally substituted. Heterocyclo is defined in ¶69 and can be optionally substituted. Heteroaryl is defined in ¶71 and can be optionally substituted. Finally, (heterocyclo)alkyl and (heteroaryl)alkyl are defined in ¶78 and with reference to the definitions for heterocyclo and heteroaryl in ¶¶ 69 and 71 respectively, also can be optionally substituted. While applicants contend that the definitions in the specification make it clear that these substituents can be optionally substituted (and thus inherently bear that interpretation throughout claim 1), on the basis of these definitions and in order to respond specifically to the Examiner's concern in this specific instance, R^2 in claim 1 has been amended to clarify that each of the recited substituents can be optionally substituted. In addition, the use of a substituted pyridyl for R^2 is described specifically on pages 11 and 13 of the application.

The Office Action contends that claims 2 and 8 lack an antecedent. Based on the amendment to claim 1 the premise of this rejection is no longer correct. Claims 1 and 7, as amended, now expressly (rather than implicitly) account for the optional substitution of the ring substituent.

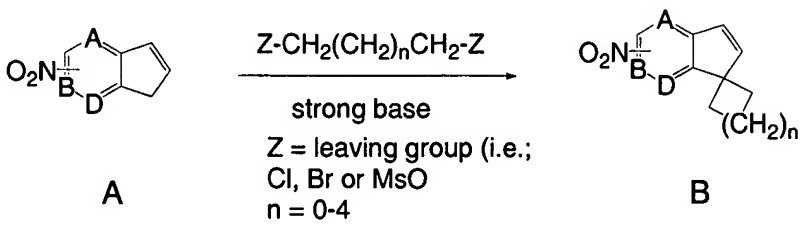
Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph, because of the inclusion of prodrugs in these claims. As noted above, reference to prodrug has been removed from the claims. The basis of this rejection no longer exists, so the rejection should be withdrawn.

Claims 1-3, 5, 7-9, 11 and 13-15 stand rejected under 35 U.S.C. 112, first paragraph, purportedly because the application does not describe how to make compounds where R^5 and R^6 form a ring. This rejection is respectfully traversed.

Preparation of compounds having a spiro structure is well within the skill in the art using techniques described in the literature well before the filing of the application on the present invention. In particular, compounds of the present invention (US patent application No 10/004,867) where R^5 and R^6 form a 3- to 7-membered carbocyclic ring may be prepared as

described in the following Scheme 1, using a reaction technique several decades old and long understood by skilled workers.

Scheme 1

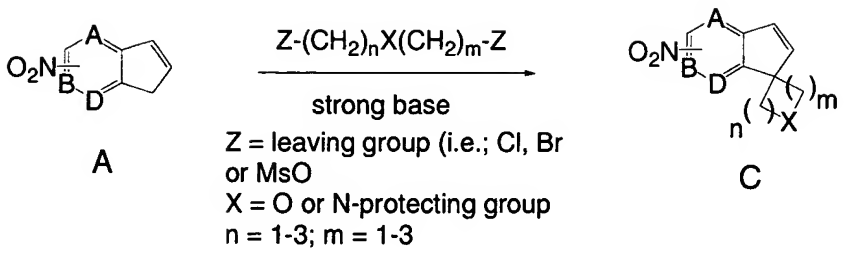


A B

Indene compound A is prepared using procedures described in the application. Compound A then may be made to react with a compound of formula $Z\text{-}CH_2(CH_2)_nCH_2\text{-}Z$ where Z is a leaving group such as Br, Cl or OMs and n is an integer from 0 to 4 in the presence of a strong base (i.e.; sodium hydride, sodium hydroxide, lithium bis(trimethylsilyl)amide or *n*-butyl lithium) in a solvent such as tetrahydrofuran or 1,2-dimethoxyethane or under phase transfer conditions to provide the spiro compound B. For example, 1*H*-Indene may be made to react with 1,2-dibromoethane in the presence of sodium hydride in 1,2-dimethoxyethane to provide the spiro cyclopropane derivative as described in *J. Amer. Chem. Soc.* **1972**, *94*, 4247-4255. 1*H*-Indene may be made to react 1,4-di-bromobutane under phase transfer conditions to provide the spiro cyclopentance derivative as described in *Tetrahedron Lett.* **1966**, 4621-4624. Thereafter, product B may be further manipulated as described in the application to provide compounds of the present invention. Such reactions are well within the skill of the art.

In a similar fashion, it also was well-within the skill of the art, at the time the subject application was filed, to prepare compounds of the present invention (US patent application No 10/004,867) where R^5 and R^6 form a 3- to 7-membered heterocyclic ring. One art-recognized approach is illustrated in the following Scheme 2.

Scheme 2



Indene compound A, again prepared using procedures described in the application, may be made to react with a compound of formula $Z\text{-}(CH_2)_nX(CH_2)_m\text{-}Z$ where Z is a leaving group such as Br, Cl or OMs, X is a heteroatom (i.e.; oxygen) or a protected heteroatom (i.e.; N-Boc or N-benzyl), n is an integer from 1 to 3 and m is an integer from 1 to 3 where the sum of n and m is less then or equal to 5 in the presence of a strong base (i.e.; sodium hydride, sodium hydroxide, lithium bis(trimethylsilyl)amide or *n*-butyl lithium) in a solvent such as tetrahydrofuran or 1,2-dimethoxyethane or under phase transfer conditions to provide the spiro product C. As with the technique of Scheme 1, this methodology has also been described in the literature before the filing of the subject application. For example, 1*H*-Indene may be made to react with bis-(2-chloro-ethyl)-carbamic acid tert-butyl ester in the presence of lithium bis(trimethylsilyl)amide in tetrahydrofuran to provide the spiro piperidine derivative as described in *J. Med. Chem.* **1992**, *35*, 2033-2039. See also *J. Med. Chem.* **1994**, *37*, 2574-2582. 1*H*-Indene may be made to react with bis-(2-chloro-ethyl)ether or bis-(2-methanesulfonyloxy-ethyl)-ether in the presence of *n*-butyl lithium in hexane and/or tetrahydrofuran to provide the spiro tetrahydropyran derivative as described in *J. Chem. Soc. Dalton Trans.* **1998**, *10*, 1607-1612. Thereafter, product C may be further manipulated as described in the application to provide compounds of the present invention. As above, such techniques were within the synthesis arsenals of skilled workers prior to the filing of the present invention.

Therefore, when the teachings of the present invention are viewed from the perspective of the skilled worker, as such teachings are to be viewed, it is clear that skilled workers are able to practice the full scope of the pending claims. Applicants respectfully submit that claims are enabled, and request that the rejection of these claims under 35 U.S.C. §112, first paragraph be withdrawn.

On the basis of the foregoing, prompt consideration of claims 1-17 in the subject application is respectfully requested.

Respectfully submitted,

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